

IN THE SPECIFICATION:

Please replace the paragraph beginning at page 4, line 23, with the following rewritten paragraph:

wherein Q is -O-, -S-, -N(R⁷)-, -(CH₂)_m-, -C(O)-, -CH(OH)-, -(CH₂)_mO-, -(CH₂)_mS-, -(CH₂)_mN(R⁷)-, -O(CH₂)_m-, -CHX^a-, -CX^a₂-, -S-(CH₂)_m-, and -N(R⁷)(CH₂)_m-, where m= 1-3, and X^a is halogen; and

Please replace the paragraph beginning at page 6, line 11, with the following rewritten paragraph:

The present invention is also directed to pharmaceutically acceptable salts of formula I. Suitable pharmaceutically acceptable salts are well known to those skilled in the art and include basic salts of inorganic and organic acids, such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, ~~methanesulphonic~~ methanesulfonic acid, trifluoromethanesulfonic acid, benzenesulfonic acid, *p*-toluenesulfonic acid, 1-naphthalenesulfonic acid, 2-naphthalenesulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, and mandelic acid. In addition, pharmaceutically acceptable salts include acid salts of inorganic bases, such as salts containing alkaline cations (e.g., Li⁺ Na⁺ or K⁺), alkaline earth cations (e.g., Mg⁺², Ca⁺² or Ba⁺²), the ammonium cation, as well as acid salts of organic bases, including aliphatic and aromatic substituted ammonium, and quaternary ammonium cations, such as those arising from protonation or peralkylation of triethylamine, *N,N*-diethylamine, *N,N*-dicyclohexylamine, lysine, pyridine, *N,N*-dimethylaminopyridine (DMAP), 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

Please replace the paragraph beginning at page 13, line 8, with the following rewritten paragraph:

It will be appreciated by those skilled in the art that the particular method of

administration will depend on a variety of factors, all of which are considered routinely when administering therapeutics. It will also be appreciated by one skilled in the art that the specific dose level for a given patient depends on a variety of factors, including specific activity of the compound administered, age, body weight, health, sex, diet, time and route of administration, rate of excretion, etc. It will be further appreciated by one skilled in the art that the optimal course of treatment, ~~ie.~~ i.e., the mode of treatment and the daily number of doses of a compound of Formula I or a pharmaceutically acceptable salt thereof given for a defined number of days, can be ascertained by those skilled in the art using conventional treatment tests.

Please replace the paragraph beginning at page 13, line 23, with the following rewritten paragraph:

The entire ~~enclosure~~ disclosure of all applications, patents and publications cited above and below are hereby incorporated by reference, including provisional application Serial No. 60/115,877, filed January 13, 1999 ~~and non-provisional application Serial No. 09/257,266 filed February 25, 1999.~~

Please replace the paragraph beginning at page 23, line 15, with the following rewritten paragraph:

Step 3. Synthesis of 5-(4-aminophenoxy)isoindoline-1,3-dione

A solution of 5-(4-nitrophenoxy)isoindoline-1,3-dione (0.6 g, 2.11 mmol) in conc. AcOH (12 mL) and water (0.1 mL) was stirred under a stream of argon while iron powder (0.59 g, 55.9 mmol) was added slowly. This mixture stirred at room temp. for 72 h, then was diluted with water (25 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried (MgSO₄) and concentrated under reduced pressure to give 5-(4-aminophenoxy)isoindoline-1,3-dione as a brownish solid (0.4 g, 75%): TLC (50% EtOAc/50% hexane) R_f 0.27; ¹H NMR (DMSO-d₆) δ 5.14 (br s, 2H), 6.62 (d, J=8.7 Hz, 2H), 6.84 (d, J=8.7 Hz, 2H), 7.03 (d, J=2.1 Hz, 1H), 7.23 (dd, 1H), 7.75 (d, J=8.4 Hz, 1H), 11.02 (s, 1H); HPLC ES-MS m/z 255 ((M+H)⁺, 100%).

Please replace the paragraph beginning at page 25, line 20, with the following rewritten paragraph:

A6. General Method for the Synthesis of Anilines from Hydroxyanilines by *N*-Protection, Nucleophilic ~~Aromatic~~ Substitution and Deprotection. Synthesis of 4-(2-(*N*-Methylcarbamoyl)-4-pyridyloxy)-2-chloroaniline

Please replace the paragraph beginning at page 29, lines 2, with the following rewritten paragraph:

A8. General Method for Synthesis of ω -Alkoxy- ω -carboxyphenyl Anilines. Synthesis of 4-(3-(*N*-Methylcarbamoyl)-~~(*N*-Methylearbamoyl)~~-4-methoxyphenoxy)aniline.

Please replace the paragraph beginning at page 28, line 19, with the following rewritten paragraph:

Step 3. 4-(3-(*N*-Methylcarbamoyl)-~~(*N*-Methylearbamoyl)~~-4-methoxyphenoxy)-1-nitrobenzene:

Please replace the paragraph beginning at page 29, line 1, with the following rewritten paragraph:

To a solution of 4-(3-carboxy-4-methoxyphenoxy)-1-nitrobenzene (0.50 g, 1.75 mmol) in CH₂Cl₂ (12 mL) was added SOCl₂ (0.64 mL, 8.77 mmol) in portions. The resulting solution was heated at the reflux temp. for 18 h, cooled to room temp., and concentrated under reduced pressure. The resulting yellow solids were dissolved in CH₂Cl₂ (3 mL) then the resulting solution was treated with a methylamine solution (2.0 M in THF, 3.5 mL, 7.02 mmol) in portions (CAUTION: gas evolution), and stirred at room temp. for 4 h. The resulting mixture was treated with a 1N NaOH solution, then extracted with CH₂Cl₂ (25 mL). The organic layer was dried (Na₂SO₄) and concentrated under reduced pressure to give 4-(3-(*N*-methylcarbamoyl)-~~(*N*-Methylearbamoyl)~~-4-methoxyphenoxy)-1-nitrobenzene as a yellow solid (0.50 g, 95%).

Please replace the paragraph beginning at page 29, line 4, with the following

rewritten paragraph:

Step 4. 4-(3-(~~N-Methylcarbamoly~~) (N-Methylcarbamoyl)-4-methoxyphenoxy)aniline:

A slurry of 4-(3-(N-methylcarbamoyl)-4-methoxyphenoxy)-1-nitrobenzene (0.78 g, 2.60 mmol) and 10% Pd/C (0.20 g) in EtOH (55 mL) was stirred under 1 atm of H₂ (balloon) for 2.5 d, then was filtered through a pad of Celite[®]. The resulting solution was concentrated under reduced pressure to afford 4-(3-(N-methylcarbamoyl)-4-methoxyphenoxy)aniline as an off-white solid (0.68 g, 96%): TLC (0.1% Et₃N/99.9% EtOAc) R_f 0.36.

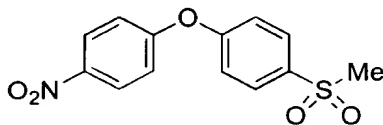
Please replace the paragraph beginning at page 33, line 15, with the following rewritten paragraph:

Step 2. Synthesis of 4-(1-isoindolinon-5-yloxy)-1-nitrobenzene

To a slurry of NaH (0.39 g, 16.1 mmol) in DMF at 0 °C was added 5-hydroxyisoindolin-1-one (2.0 g, 13.4 mmol) in portions. The resulting slurry was allowed to warm to room temp. and was stirred for 45 min., then 4-fluoro-1-nitrobenzene was added and then the mixture was heated at 70 °C for 3 h. The mixture was cooled to 0 °C and treated with water dropwise until a precipitate formed. The resulting solids were collected to give 4-(1-isoindolinon-5-yloxy)-1-nitrobenzene as a dark yellow solid (3.23 g, 89%): TLC (100% EtOAc) R_f 0.35.

Please replace the paragraph beginning at page 40, line 14, with the following rewritten paragraph:

A19. Synthesis of ω-Sulfonylphenyl Anilines. Synthesis of 4-(4-Methylsulfonylphenoxy)aniline.



Step 1. 4-(4-Methylsulfonylphenoxy)-1-nitrobenzene: To a solution of 4-(4-methylthiophenoxy)-1-nitrobenzene (2.0 g, 7.7 mmol) in CH₂Cl₂ (75 mL) at 0 °C was slowly added *m*-CPBA (57-86%, 4.0 g), and the reaction mixture was stirred at room temperature for 5 h. The reaction mixture was treated with a 1N NaOH solution (25

mL). The organic layer was sequentially washed with a 1N NaOH solution (25 mL), water (25 mL) and a saturated NaCl solution (25 mL), dried (MgSO₄), and concentrated under reduced pressure to give 4-(4-methylsulfonylphenoxy)-1-nitrobenzene as a solid (2.1 g).

Please replace the paragraph beginning at page 47, line 19, with the following rewritten paragraph:

C3. Combinatorial Method for the Synthesis of Diphenyl Ureas Using Triphosgene

One of the anilines to be coupled was dissolved in dichloroethane (0.10 M). This solution was added to a 8 mL vial (0.5 mL) containing dichloroethane (1 mL). To this was added a bis(trichloromethyl) carbonate solution (0.12 M in dichloroethane, 0.2 mL, 0.4 equiv.), followed by diisopropylethylamine (0.35 M in dichloroethane, 0.2 mL, 1.2 equiv.). The vial was capped and heated ~~heat~~ at 80 °C for 5 h, then allowed to cool to room temp for approximately 10 h. The second aniline was added (0.10 M in dichloroethane, 0.5 mL, 1.0 equiv.), followed by diisopropylethylamine (0.35 M in dichloroethane, 0.2 mL, 1.2 equiv.). The resulting mixture was heated at 80 °C for 4 h, cooled to room temperature and treated with MeOH (0.5 mL). The resulting mixture was concentrated under reduced pressure and the products were purified by reverse phase HPLC.

Please replace the paragraph beginning at page 49, line 1, with the following rewritten paragraph:

D. Interconversion of Ureas

D1a. Conversion of ω -Aminophenyl Ureas into ω -(~~Arylamino~~ Arylamino)phenyl Ureas. Synthesis of *N*-(4-Chloro-3-((trifluoromethyl)phenyl)-*N'*-(4-(3-methoxycarbonylphenyl)carboxyaminophenyl) Urea

Please replace the paragraph beginning at page 56, line 4, with the following rewritten paragraph:

Entry 15: According to Method C2d, 5-(~~trifluoromethyl~~ ~~triflouromethyl~~)-2-methoxyaniline was reacted with CDI followed by 4-(3-*N*-methylcarbamoyl)-4-methoxyphenoxy)aniline, which had been prepared according to Method A8, to afford the urea.